

*REMARKS/ARGUMENTS**Amendments to the Drawings*

The Examiner is requested to approve the accompanying replacement drawings. As noted above, Figs. 2 and 5 have been amended to include statements that explain the meaning of the asterisks depicted therein. The amendments to the drawings are fully supported by the specification as originally filed, e.g., at paragraph [0030]. No new matter has been added.

Amendment to the Specification

Paragraph [0030] has been amended to clarify the meaning of the asterisks referenced therein.

Amendments to the Claims

The claims have been amended to point out more particularly and distinctly claim the invention. Claims 1-3 also have been amended to recite prophylactic administration of vinpocetine, and claim 4, which recites a method for preventing epileptic seizures, has been amended to read as an independent claim. Claims 5-8 have been canceled.

Office Action

The drawings have been objected to under 37 C.F.R. § 1.83(a) as allegedly failing to describe what the asterisks stand for.

Claims 1-8 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nekrassov et al., *Brain Research*, 868, 222-229 (2000) ("Nekrassov et al.") in view of Hotz et al., *Eur. Arch. Otorhinolaryngol.*, 247, 202-205 (1990) ("Hotz et al.") and U.S. Patent No. 4,882,336 ("Tigyi et al.").

Discussion of the Office Action

With regard to the drawings, as noted above, Figs. 2 and 5 have been amended to clarify the meaning of the asterisks referenced therein. Paragraph [0030] also has been amended to clarify the meaning of the asterisks. The amendment of Figs. 2 and 5, and the amendment of paragraph [0030], are believed to render moot the objection to the drawings. Accordingly, withdrawal of the objection to the drawings and approval thereof are respectfully solicited.

With regard to the obviousness rejection, Applicant respectfully submits that the cited references, alone or in combination, do not disclose or suggest administering vinpocetine in accordance with the claimed methods. In the studies disclosed by Nekrassov et al. and Hotz et al., aminoglycoside antibiotics increased wave I and other waves latencies. Aminoglycoside antibiotics damage peripheral structures, as shown by the alterations in the first wave (wave I in humans or P1 in animals). Auditory evoked potentials are commonly referred as “brainstem auditory evoked potentials (BAEPs)” or “auditory brainstem responses (ABRs),” but this does not mean that all the waves of those potentials originate from nuclei at the brainstem level. Aminoglycoside antibiotics are unable to change directly the physiology of the brainstem retro-cochlear nuclei generating the later ABR waves. Although, the changes resulting from damage of the inner ear function induced by the chronic treatment with the aminoglycoside antibiotics can indirectly affect other ABR waves. In contrast, the acute changes in the later ABR waves linked to epilepsy cannot change indirectly the more peripheral waves (such as wave I). Therefore, the novelty of the findings supporting the present patent application, which shows that acute vinpocetine prevents the hearing loss linked to alterations of the later ABR waves observed during epilepsy, are not disclosed or suggested by Nekrassov et al. or Hotz et al.

In 2003, the present inventors published the first evidence showing that epilepsy can induce hearing loss by changing the ABR retro-cochlear waves originating in brainstem nuclei of the auditory tract. See Nekrassov et al., *Epilepsy Research*, 53, 245-254 (2003) (“Nekrassov et al. 2003”), a copy of which was provided with Applicant’s previous response. The claims of the present application are directed to the use of vinpocetine in the prevention of the auditory complications induced by epilepsy based on Applicant’s discovery that vinpocetine prevented the hearing loss resulting from the alterations in the ABR waves generated in brainstem nuclei of the auditory tract during seizures in two different experimental animal models of epilepsy.

In view of the fact that in the experimental animal models of epilepsy the first wave of the ABR was unchanged (Nekrassov et al. 2003) and that in Nekrassov et al., the amikacin-induced ototoxicity triggered by alterations in P1 wave generators observed after a long time period only was inhibited after a chronic vinpocetine post-treatment, the vinpocetine prevention of hearing loss induced by the alterations in audition linked to the acute changes in brainstem nuclei physiology observed during seizures was unpredictable. In fact, the

Applicant's goal at that time was to test the neuroprotective action of vinpocetine in a manifestation of brain damage like the epileptiform activity (EEG), and as those equipments were particularly designed to study evoked potentials, the Applicant also recorded the ABR by curiosity, with the surprising findings that led to the discovery of the presently claimed method treating epileptic patients.

In this regard, Applicant respectfully submits that the cited art does not support the Office's argument that one of ordinary skill in the art could have conceived of the claimed method, as before Applicant's work, there is no evidence that anyone skilled in that art even had an expectation that vinpocetine could have been successfully used in accordance with the claimed method. There was no reason to think that a drug capable of preventing hearing loss triggered by alterations involving more peripheral anatomical structures, such as the cochlea or the auditory nerve, could have been useful for preventing hearing loss induced by alterations in other brain structures of the auditory tract. In summary, before testing the effect of a drug (vinpocetine) on the epileptic activity-induced changes in electroencephalogram (EEG) and ABR, it was impossible to predict that the same drug could be useful to prevent hearing loss of such a different etiology. The method of treating demyelination clinical patterns of autoimmune origin in an animal subject with a therapeutically effective amount of vinpocetine disclosed by Tigyi et al. does not disclose or suggest, alone or in combination with Nekrassov et al. and/or Hotz et al., the claimed method, in which vinpocetine is used for completely different physiological alterations.

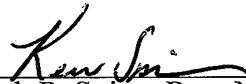
As noted previously, a judgment on obviousness may only involve some level of hindsight so long as it does not rely on knowledge gleaned only from an applicant's disclosure (M.P.E.P. § 2145(X)(4)). In other words, "[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998). Simply stated, "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Thus, it is improper to pick and choose from among isolated disclosures in the prior art to arrive at the claimed invention using the benefit of Applicant's disclosure as a guide, particularly when there is no evidence that anyone prior to Applicant's discovery had heretofore discovered the claimed method, which the cited art fails to disclose or suggest.

Accordingly, Applicant respectfully submits that the amended claims are not obvious in view of the cited references. For at least the foregoing reasons, withdrawal of the obviousness rejection is respectfully solicited.

Conclusion

Applicant respectfully submits that the present application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: June 4, 2010